An emerging trend in functional foods for the prevention of cardiovascular disease and diabetes: Marine algal polyphenols

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To cite this article: Margaret Murray, Aimee L. Dordevic, Lisa Ryan & Maxine P. Bonham (2016): An emerging trend in functional foods for the prevention of cardiovascular disease and diabetes: Marine algal polyphenols, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2016.1259209

To link to this article: http://dx.doi.org/10.1080/10408398.2016.1259209

Accepted author version posted online: 11 Nov 2016.
Published online: 11 Nov 2016.
An emerging trend in functional foods for the prevention of cardiovascular disease and diabetes: Marine algal polyphenols

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ABSTRACT
Marine macroalgae are gaining recognition among the scientific community as a significant source of functional food ingredients. Due to the harsh environments in which macroalgae survive, they produce unique bioactive compounds that are not found in terrestrial plants. Polyphenols are the predominant bioactive compound in brown algae and are accountable for the majority of its biological activity. Phlorotannins are a type of polyphenol that are unique to marine sources and have exhibited protective effects against hyperglycemia, hyperlipidemia, inflammation and oxidative stress, known risk factors for cardiovascular disease and diabetic complications. This review updates the information on marine polyphenols, with a particular focus on phlorotannins and their potential health benefits in relation to the prevention and treatment of risk factors for type 2 diabetes and cardiovascular diseases.

Introduction
Polyphenols are a highly heterogeneous group of compounds (Naczk and Shahidi 2004) that are synthesized in terrestrial plants (Manach et al. 2004; Naczk and Shahidi 2004) and marine algae (Murugan et al. 2015). Their natural function is predominantly to act as the defense system of the organism, protecting against ultra-violet radiation (Manach et al. 2004; Naczk and Shahidi 2004; Bocanegra et al. 2009; Heffernan et al. 2015), infection (Manach et al. 2004; Naczk and Shahidi 2004; Heffernan et al. 2015), and consumption by herbivores (Bocanegra et al. 2009; Heffernan et al. 2015). Over 8000 structurally different polyphenols have been identified, from simple monomer units to complex polymerized structures (Kris-Etherton et al. 2002; Crozier et al. 2009). However, only several hundred of those varieties exist in edible plants (Manach et al. 2004), and those from terrestrial sources have been extensively reviewed (Scalbert and Williamson 2000; Yang et al. 2001; Kris-Etherton et al. 2002; Higdon and Frei 2003; Manach et al. 2004; Naczk and Shahidi 2004; Bocanegra et al. 2009; Manach et al. 2005; Williamson and Manach 2005; D’Archivio et al. 2007; Crozier et al. 2009). This review investigates polyphenols from marine macroalgae, their dietary intake levels and key dietary sources, their potential as functional food ingredients and potential role as mediators of cardiovascular disease and diabetes.

A variety of polyphenols, including catechins, flavonoids, and phlorotannins, can all be found in marine macroalgae (Murugan et al. 2015). However, phlorotannins, the predominant polyphenol in macroalgae, are unique to marine sources (Heffernan et al. 2015). Phlorotannins are synthesized in marine macroalgae through the acetate-malonate pathway by the polymerization of phloroglucinol monomer units (1,3,5-tri hydroxybenzene) (Shibata et al. 2004; Chowdhury et al. 2014; Heffernan et al. 2015; Murugan et al. 2015) (Figure 1). Phlorotannins are highly hydrophilic molecules that contain both phenyl (C₆H₅-) and phenoxy (C₆H₅O-) groups (Figure 1) and range in size from 126 Da to 650 kDa (Murugan et al. 2015), a much broader range than terrestrial polyphenols (up to 30 kDa) (Bravo 1998). Phlorotannins vary in structure and degree of polymerization (Bocanegra et al. 2009), and are classified into four subclasses based on the chemical bonds they contain (Murugan et al. 2015). The subclasses are 1) fucols which have a phenyl linkage; 2) fuhalols and phlorethols which contain an ether linkage; 3) fucochloroethols which have a mixture of a phenyl and ether linkage; and 4) eckols which contain a dibenzodioxin linkage (Figure 1) (Murugan et al. 2015). However, the literature often defines phlorotannins based on their source or specific type (e.g. Chlorofucofuroeckol A, dieckol) rather than which subclass they belong to.

Sources
There exist around 10,000 species of marine macroalgae, which are classified into three categories based on their pigmentation; Chlorophyta (green algae), Rhodophyta (red algae), and Phaeophyta (brown algae). Of the three varieties, brown algae contain the highest levels of polyphenols (Bocanegra et al. 2009; Heffernan et al. 2015) (5-30% of the dry weight (Heffernan et al. 2015)) the majority of which are phlorotannins (Chowdhury et al. 2014; Hamed et al. 2015). Due to the harsh environments in which marine macroalgae exist, including exposure to varying...
light intensity, salinity, pressure and temperatures, they produce a variety of unique and potent bioactive substances, which are not found in terrestrial plants (Hamed et al. 2015).

Different algal species contain varying combinations and concentrations of phlorotannins, and within a single species of marine alga a range of low and high molecular weight phlorotannins can be found (Heffernan et al. 2015) (Table 1). Phlorotannin content can vary between individuals of the same algal population, even within an individual algal body (Bocanegra et al. 2009) and phlorotannins are generally more concentrated in the outer layers of the organism, where it is exposed to the environment (Shibata et al. 2004). Environmental factors such as ultraviolet radiation, salinity, light and nutrient availability and herbivore grazing are likely causes for differences in phlorotannin content (Bocanegra et al. 2009). The location on the shore at which brown algae is grown may also affect phlorotannin content. Species grown in the intertidal zones have the highest phlorotannin content, whereas those grown at lower and upper levels of the shore have lower phlorotannin content (Connan et al. 2004), likely due to differences in exposure to environmental factors. The phlorotannin content of brown algae also varies according to season, and the degree of seasonal variation differs among species (Connan et al. 2004). The Fucales genus, Pelvetia canaliculata and Ascophyllum nodosum species exhibit maximal phenolic content in summer, whereas the Laminariales genus has a higher content in winter, and Fucus vesiculosus and Ecklonia radiata have highest levels in spring (Steinberg 1995; Connan et al. 2004).

Due to the structural complexity and polymeric nature of phlorotannins—variations in the number of monomer units, their positions, and chemical bonds with which they are joined—there is currently limited understanding of the array of phlorotannins in marine algae, and the distribution of phlorotannins within specific algal species (Heffernan et al. 2015). Historically, only low molecular weight phlorotannins (2-8 phloroglucinol units) could be characterized and the isomeric complexity of high molecular weight phlorotannins was unable to be elucidated (Heffernan et al. 2015). However, recent technological advancements in chromatographic and mass spectrometric techniques allow for more thorough study of the complex structures and distribution of phlorotannins in marine algae, with phlorotannin isomers of up to 16 monomer units successfully detected (Heffernan et al. 2015).

**Phlorotannin intake**

There is currently no known literature that outlines average population intake of marine phlorotannins. However, macroalgae consumption is documented in Asian countries, such as Japan, where it is a traditional part of the diet (Besada et al. 2009; Mouritsen et al. 2013). In 2006, Japanese households consumed 450 g per year of the seaweed Kombu (Laminaria japonica—a brown macroalgae), although generally consumption was four times higher in elders than in young adults (< 29 years) (Zava and Zava 2011). However, while Kombu consumption has decreased over the last 50 years in Japan, daily seaweed intake has remained relatively stable; 4.3 g/day in 1955 and 5.3 g/day in 1995 with an increase in Wakame (Undaria pinnatifida—a brown macroalgae) and Nori (Porphyra genus—a red algae) varieties making up for the decline in Kombu (Zava and Zava 2011). An average intake of 5.3 g of seaweed per day equates to approximately 160 mg of phlorotannins per day from seaweed (Connan et al. 2004; Shibata et al. 2004), however, this value would vary depending on individual intake, seaweed variety and bioavailability. From the red alga family, Porphyra is the genus that is most frequently consumed (Nori). From the brown algae, the Laminaria japonica (Kombu), Undaria pinnatifida (Wakame) and Hizikia fusiforme (Hiziki) species are the most commonly consumed (Besada et al. 2009; Zava and Zava 2011).
In most western cultures, seaweed is relatively new to the diet, but consumption has been steadily increasing since the early 1980s (Besada et al. 2009; Mouritsen et al. 2013) due to consumer demand for interesting, natural and sustainable food products (Mouritsen et al. 2013). However, there is limited literature regarding actual daily intakes of seaweed among western cultures. The red seaweed *Palmaria palmata* is common in Atlantic waters and is one of the few algal species that is documented to have been used for human consumption in Europe (Mouritsen et al. 2013). However, there are now polyphenol-rich seaweed extracts that are commercially available as health food products in the United States of America, Canada and Korea. These supplements may dramatically increase the average population intake of marine polyphenols in these countries. Especially as these products carry claims of antioxidant and anti-inflammatory activity, improvement of lipid balance, weight loss and protection against cardiovascular disease and diabetes. These claims are as yet unsubstantiated in human populations, but there is some support for their role in certain health outcomes based on evidence from *in vitro* and animal studies.

Accurate estimation of polyphenol intake based on dietary intake data, like any other dietary component, is difficult. Collection of dietary data is predominantly through self-report and therefore is likely to be inexact and carry bias. Perceived ‘unhealthy’ foods are often under-reported, while perceived ‘healthy’ foods are typically over-reported (Spencer et al. 2008),
resulting in an overestimation of polyphenol intake. The difficulty of estimating polyphenol intake is further exacerbated as the polyphenol content of foods is not included in most food composition databases. There is an online European database that provides information on the polyphenol content of 459 common foods, but as yet this is limited to polyphenols from terrestrial food sources (includes 500 different polyphenols) and does not include phlorotannins (Phenol-Explorer, Version 3.6, http://phenol-explorer.eu/). Furthermore the variation in terrestrial food sources (includes 500 different polyphenols) common foods, but as yet this is limited to polyphenols from that provides information on the polyphenol content of 459 composition databases. There is an online European database the polyphenol content of foods is not included in most food difficulty of estimating polyphenol intake is further exacerbated as species increases the difficulty of accurate intake estimation, as the recorded phlorotannin content of seaweeds in food databases may not be an accurate representation of all individuals in that species. The use of biomarkers, such as urinary excretion or plasma levels of polyphenols, are becoming more widely used may be more useful measures to determine polyphenol intake and make conclusions about the potential health effects of polyphenols (Wang et al. 2015).

**Potential of marine algal polyphenols as a functional food**

A functional food or functional ingredient is defined as a “natural or processed food that contains known or unknown biologically-active compounds; which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease” (Martirosyan and Singh 2015). The value of seaweeds, and their constituents, as functional food products is rapidly increasing as science uncovers their many biological activities and potential health benefits. There are also a number of benefits to utilizing marine sources, as opposed to land-based sources, to attain biologically active compounds. Recent trends have shown an increase in consumer preferences for natural and sustainable health products and functional foods (Blandon et al. 2007; Mouritsen et al. 2013), thus there is interest in marine-based food products (Murugan et al. 2015). With the ocean making up more than 70% of the Earth’s surface (Hamed et al. 2015), it provides an abundant source of marine products, and algal species are easy to harvest from the wild as well as to culture in the sea and in pools on land (Mouritsen et al. 2013). The cultivation of marine algae has a number of advantages over terrestrial plant cultivation; it requires less fresh water, produces a higher biomass, can be grown in lower quality agricultural environments, and can be grown in seawater avoiding the need for herbicides and pesticides (Buono et al. 2014).

In addition, recent advances in biotechnological tools for the extraction and identification of bioactive compounds from marine algae, has led to an upward trend in the use of these products as functional food ingredients (Murugan et al. 2015). Therefore there is likely to be a large market for marine polyphenols as a functional food ingredient if efficacy can be demonstrated.

While drugs are the current accepted treatment for blood sugar and cholesterol control, long term use of oral antidiabetic and anti-hyperlipidemic drugs can cause unpleasant side effects, including muscle cramping, fatigue, muscle breakdown, vomiting and diarrhea (Golomb and Evans 2008; Di Stasi et al. 2010; Bahadoran et al. 2013; Murugan et al. 2015). Whereas marine polyphenols are thought to be relatively safe for consumption (Zaragoza et al. 2008; Heo et al. 2009; Yeo et al. 2012; Yang et al. 2014; Kang et al. 2015; Kellogg et al. 2015) and lack unpleasant side effects (Paradis et al. 2011; Bahadoran et al. 2013; Murugan et al. 2015). The safety of a polyphenol-rich supplement from Fucus vesiculosus has been demonstrated at up to 750 mg/kg/day, in rats, over four weeks (Zaragoza et al. 2008). The phlorotannin diphenylethohydroxyxycarmalol (DPHC) has also shown no cytotoxicity in human umbilical vein epithelial cells (HUVECs) at concentrations up to 3.91 mM after 20 hours incubation (Heo et al. 2009). It should be noted, however, that green tea polyphenols have been shown to cause hepatotoxicity and other adverse effects at high doses; 500 mg/kg/day of pure epigallocatechin gallate (EGCG) for 13 weeks increased bilirubin and decreased fibrinogen in rats. The risk of toxicity is increased when ingested in the fasting state or over long periods of time, or when the polyphenols are administered intraperitoneally to animals (Mazzanti et al. 2009). If the safety of marine polyphenols and efficacy for blood glucose or cholesterol control, or inflammation reduction can be shown in a human population, then marine polyphenols have great potential for commercialization as a functional food ingredient.

**Marine algal polyphenols and chronic disease**

Polyphenols from seaweeds are thought to help reduce hyperglycemia, hyperlipidemia, oxidative damage, and chronic inflammation; metabolic abnormalities that increase the risk of cardiovascular diseases (CVDs) and diabetic complications (Bahadoran et al. 2013). Polyphenols from terrestrial sources have been linked to positive health effects regarding a number of risk factors for chronic conditions including obesity, diabetes and cardiovascular diseases (Kris-Etherton et al. 2002; Higdon and Frei 2003; Crozier et al. 2009; Hursel et al. 2009; Hanhineva et al. 2010; Hursel et al. 2011; Rains et al. 2011; Bahadoran et al. 2013). Recent research has extended to marine macroalgae, possibly as a result of epidemiological data from Asian countries which indicate a diet rich in seaweed is associated with longevity and a decreased risk for cardiovascular disease, some cancers, and other chronic diseases (Miyagi et al. 2003; Willcox et al. 2009; Gavrilo and Gavrilov 2012).

**Anti-hyperglycemic effects**

Impaired carbohydrate metabolism, insulin resistance, increased gluconeogenesis, β-cell dysfunction, and defects in insulin signaling pathways are all potential causes of hyperglycemia and risk factors for type 2 diabetes (Bahadoran et al. 2013). Both acute and chronic high blood glucose cause overloading of the metabolic pathways with glucose, resulting in oxidative stress and free radical formation, cardiovascular disorders, nephropathy, retinopathy, neuropathy, foot and leg ulcers, and limb amputation (Barde et al. 2015; Murugan et al. 2015). Alpha-amylase, located in the pancreas, and α-glucosidase, at the brush border of intestinal cells, are two key enzymes involved in carbohydrate metabolism (Kim et al. 2000; Benalla et al. 2010; Murugan et al. 2015). These enzymes break down carbohydrates into monosaccharides that are absorbed into the bloodstream, resulting in a rise in blood glucose following a
meal (Kim et al. 2000; Benalla et al. 2010; Murugan et al. 2015). Enzyme inhibition reduces the rate at which glucose is released from carbohydrate foods following a meal, and can be an effective strategy for managing postprandial blood glucose (Kim et al. 2000; Benalla et al. 2010; Murugan et al. 2015). Oral glucosidase inhibitor drugs are the common clinical treatment for type 2 diabetes, however, long-term use can result in side effects such as renal tumors, acute hepatitis and serious hepatic injury (Murugan et al. 2015). Marine polyphenols may be a safer alternative (Heo et al. 2009; Paradis et al. 2011; Bahadoran et al. 2013; Murugan et al. 2015).

In vitro studies
One of the key mechanisms by which marine polyphenols exert protective effects against type 2 diabetes is through the inhibition of α-amylase and α-glucosidase. Polyphenolic-rich extracts from the marine macroalgae Alaria, Pulmaria, and Ascophyllum exhibited some α-amylase inhibitory activity. The extract from Ascophyllum demonstrated the strongest α-amylase inhibition (IC50 approximately 0.1 μg/mL gallic acid equivalents (GAE)) and was the only extract to also inhibit α-glucosidase activity (IC50 approximately 20 μg/mL GAE) (Nwosu et al. 2011). An Ascophyllum nodosum extract has also been shown to induce dose-dependent α-amylase and α-glucosidase inhibition (Apostolidis and Lee 2010). Furthermore, the α-glucosidase inhibition observed from the phlorotannin-rich Ascophyllum nodosum extract (0.24 μg phenolics) was greater than that of acarbose (0.37 μg), a current antidiabetic drug (Apostolidis and Lee 2010). DPHC, a phlorotannin extracted from Ishige okamurae, also dose dependently inhibited α-amylase and α-glucosidase activity (IC50 values of 0.53 and 0.16 mM, respectively) in a chemical assay to a greater extent than acarbose (Heo et al. 2009).

Marine polyphenols also act on other enzymes involved in carbohydrate metabolism to reduce hyperglycemia. The phlorotannins phlorofucofuroeckol A, dieckol and 8,8'-bieckol extracted from Eisenia bicyclus inhibited α-fucosidase, β-galactosidase and β-mannosidase, enzymes involved in carbohydrate break down, in vitro. Whereas the phlorotannins phloroglucinol, eckol and an unidentified tetramer were only weakly active against the enzymes (Shibata et al. 2002). An additional mechanism by which phlorotannins from Ascophyllum nodosum (400 μg/mL extract) have demonstrated to potentially reduce hyperglycemia is to increase basal glucose uptake in 3T3-L1 adipocytes. During a 20-minute incubation period glucose uptake increased by approximately 3-fold (Zhang et al. 2007). In addition, marine polyphenols from Ecklonia cava have been shown to activate the AMP-activated protein kinase/acetyl-CoA carboxylase (AMPK/ACC) signal transduction pathways in C2C12 myoblasts (Kang et al. 2010), which results in increased glucose uptake into the cells and is another potential mechanism for a reduction in blood glucose levels (Park et al. 2002) (Figure 2).

Animal studies
Six weeks of supplementation with a diet containing 0.5% w/w of a polyphenol-rich extract from Ishige okamurae reduced hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK) activity and increased hepatic glycogen production in mice, which resulted in reduced fasting blood glucose level (Min et al. 2011). The treated mice also presented with reduced hyperinsulinemia and HbA1c, compared with control (Min et al. 2011). Similarly, diabetic KK-A' mice that were administered 16.42 or 81.20 mg/day (0.2% or 1% of diet, respectively) of a phlorotannin extract from Ecklonia stolonifera for 4 weeks maintained blood glucose and insulin levels at a close-to-normal level in a dose-dependent manner, compared with control mice whose blood glucose and insulin levels increased over time (Iwai 2008). Kang et al (2013), also identified that supplementation with dieckol (20 mg/kg body weight/ day for 14 days), from Ecklonia cava, reduced blood glucose and insulin levels in C57BL/KsJ-db/db diabetic mice. Interestingly, a dose-dependent treatment effect on insulin levels but
not blood glucose levels was observed (Kang et al. 2013). Park et al. (2012) reported that supplementation with 200 mg/kg body weight/day of an Ecklonia cava polyphenol extract for 7 weeks reduced fasting blood glucose in obese C57BL/6 mice compared with placebo. Diabetic mice administered with 200 mg/kg body weight of a crude extract or enriched extract (purified polyphenolic fraction) from Asccophyllum nodosum for up to 4 weeks, exhibited reduced fasting blood glucose following both doses compared with placebo. However, only the enriched extract dampened the postprandial rise in blood glucose following an oral sucrose tolerance test (Zhang et al. 2007). Similarly, a dieckol-rich extract from Ecklonia cava (0.5 g/100 g diet) reduced fasting blood glucose levels, HbA1c levels and plasma insulin levels in C57BL/6/KsJ-db/db/db/db/db mice after 6 weeks, compared with a control diet (Lee et al. 2012). The effect observed from the dieckol-rich extract was comparable to that of rosiglitazone (0.005 g/100 g diet), a current antidiabetic drug. Glucose tolerance also improved in the mice as a result of phlorotannin supplementation; the blood glucose area under the curve (AUC) was significantly reduced following phlorotannin treatment compared with control (Lee et al. 2012). Obese mice administered with an Ecklonia cava phlorotannin-rich extract (28.2 ± 0.58% polyphenols) five times a week for 12 weeks (Eo et al. 2015), also presented with reduced postprandial blood glucose AUC following both the 100 mg/kg body weight/day and 500 mg/kg body weight/day doses, compared with placebo. The high dose group exhibited significantly lower plasma insulin and HOMA-IR after 12 weeks compared with placebo. However, polyphenol supplementation had no effect on fasting blood glucose (Eo et al. 2015). Furthermore, when fed to streptozotocin-induced diabetic mice, a 100 mg/kg body weight single dose of DPHC diminished postprandial blood glucose AUC to 2022 (113.0) mmol/min, compared with 2210 (125.2) mmol/min in the control mice (Heo et al. 2009).

**Human studies**

In a randomized controlled trial, Shin et al (2012) gave 97 overweight adults a daily dose of either 72 mg or 144 mg of a polyphenol-rich extract (polyphenol content 98.5%) from Ecklonia cava, or a placebo, for 12 weeks. A reduction in fasting blood glucose was observed, but only in the high dose group (Shin et al. 2012). Conversely, another randomized controlled trial showed that three months of an oral supplement (500 mg/day) containing 5% marine polyphenols increased plasma insulin levels, HOMA-β-cell and HOMA-IR, compared with placebo, in overweight and obese adults. However, no change was observed in fasting blood glucose levels or blood glucose levels following an oral glucose tolerance test (OGTT) (Hernandez-Corona et al. 2014). Lee and Jeon (2015) administered 690 mg polyphenols or a placebo to 73 adults with high fasting blood glucose (100 to 180 mg/dL) for 12 weeks. While an improvement in postprandial blood glucose control and significant reduction in fasting blood insulin levels was observed following supplementation, there was, again, no change in fasting blood glucose level. Furthermore, Paradis et al (2011) demonstrated a reduction in three hour postprandial insulin incremental area under the curve (iAUC) and increased insulin sensitivity in 23 non-diabetic adults following consumption of a phlorotannin-rich blend of the brown seaweeds Ascophyllum nodosum and Fucus vesiculosus. Participants consumed either 500 mg seaweed capsules (containing at least 10% polyphenols) or placebo capsules 30 minutes prior to 50 g of available carbohydrates from bread. There was no significant effect on postprandial blood glucose iAUC (Paradis et al. 2011).

**Summary**

Marine polyphenols inhibit the action of α-amylase and α-glucosidase in vitro, and reduce the postprandial rise in blood glucose and insulin levels in animals. However, reductions in postprandial blood glucose and insulin have not been consistently demonstrated in humans (Table 2). Marine polyphenols also reduce fasting blood glucose in animals, and one study has shown this same effect in humans (Shin et al. 2012). Some evidence suggests that a dose-dependent relationship exists between polyphenol intake and the anti-hyperglycemic effects, yet the variation in dosages, timeframes and species examined between studies make interpretation difficult.

**Anti-hyperlipidemic effects**

Dyslipidemia occurs in diabetes and contributes to CVD risk (Grundy et al. 1999; Rader 2007; Musunuru 2010, Bahadoran et al. 2013). One of the key protective activities of terrestrial polyphenols on the cardiovascular system is the improvement of dyslipidemia. Polyphenols reduce digestion and absorption of dietary lipids, decrease synthesis and secretion of apolipoprotein B, inhibit cholesterol esterification and intestinal lipoprotein production, and inhibit key enzymes in lipid biosynthesis pathways (Bahadoran et al. 2013) resulting in an improved lipid profile and lowered cardiovascular risk. Emerging research indicates that marine polyphenols may have similar lipid lowering actions.

**In vitro studies**

*In vitro* research suggests a number of mechanisms by which marine polyphenols may exert anti-hyperlipidemic activity (Figure 2). Both Seapolynol™ (a polyphenol extract containing 98.5% unspecified polyphenols) and the isolated phlorotannin dieckol from Ecklonia cava, dose dependently (0–200 μg/mL) inhibited adipocyte differentiation and lipid accumulation in 3T3-L1 preadipocytes, (which contributes to reduced intracellular triglyceride (TG) levels) and inhibited activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase (an enzyme involved in cholesterol production) in a HMGCoA reductase assay kit (Yeo et al. 2012). The phlorotannins phloroglucinol, eckol, and phlorofucofuroeckol A from Ecklonia stolonifera also dose dependently (12.5–100 μM) inhibited lipid accumulation in 3T3-L1 adipocytes and did not affect cell viability at 0–200 μM for 24 h (Jung et al. 2014). Phloroglucinol, eckol, dieckol, dioxinohydroeckol and phlorofucofuroeckol A also reduced expression levels of adipocyte marker genes peroxisome proliferator activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα), which suggests that phlorotannins regulate adipogenesis and inhibit adipocyte differentiation via modulation of PPARγ and C/EBPα expression (Jung et al. 2014). This mechanism has been suggested as a way of managing obesity via reduction of the formation of
<table>
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<td><em>Ecklonia stolonifera</em></td>
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<td><em>Ecklonia cava</em></td>
<td>Polyphenol extract (28.2 ± 0.58% polyphenols): Dieckol, 2,7''-phloroglucinol-6,6''-bieckol, Pyrygallol-phloroglucinol-6,6''-bieckol, Phlorofucofuroeckol A</td>
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<td>200 mg/kg body weight for 7 days</td>
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<td><em>Ecklonia cava</em></td>
<td>Dieckol</td>
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<td>Reduced blood glucose, Reduced plasma insulin, Reduced HbA1c</td>
<td>(Lee et al. 2012)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Dieckol</td>
<td>20 mg/kg body weight for 14 days</td>
<td>C57BL/KsJ-db/db, a type II diabetes mice</td>
<td>Reduced blood glucose, Reduced dependency of plasma insulin, Reduced G6Pase and PEPCK activity, Increased hepatic glycogen production, Reduced fasting blood glucose, Reduced HbA1c</td>
<td>(Kang et al. 2013)</td>
</tr>
<tr>
<td><em>Ishige okamurae</em></td>
<td>Does not mention specific polyphenols</td>
<td>0.5% w/w for 6 weeks</td>
<td>C57BL/KsJ-db/db mice</td>
<td>Increased insulin sensitivity, Reduced insulin resistance, Reduced glucose, Reduced HbA1c</td>
<td>(Min et al. 2011)</td>
</tr>
<tr>
<td><em>Ascophyllum nodosum, Fucus vesiculosus</em></td>
<td>Commercially available blend of brown seaweeds containing a minimum of 10% polyphenols</td>
<td>50 mg polyphenols, single dose prior to postprandial testing</td>
<td>23 non-diabetic adults</td>
<td>Reduced postprandial insulin iAUC, Increased insulin sensitivity</td>
<td>(Paradis et al. 2011)</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Seaweed species</th>
<th>Polyphenol</th>
<th>Dosage and duration</th>
<th>Subject/medium</th>
<th>Anti-diabetic effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Polyphenol extract</td>
<td>72 or 144 mg/day for 12 weeks</td>
<td>97 non-diabetic overweight adults</td>
<td>Reduced fasting blood glucose (high dose only)</td>
<td>(Shin et al. 2012)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Dieckol-rich extract</td>
<td>690 mg/day for 12 weeks</td>
<td>73 adults with high fasting blood glucose</td>
<td>Improved postprandial blood glucose control</td>
<td>(Lee and Jeon 2015)</td>
</tr>
<tr>
<td>Not specified</td>
<td>Polyphenol containing (5%) oral supplement</td>
<td>25 mg polyphenols for 3 months</td>
<td>25 non-diabetic overweight or obese volunteers</td>
<td>Increased plasma insulin, HOMA β-cell and HOMA -IR</td>
<td>(Hernandez-Corona et al. 2014)</td>
</tr>
</tbody>
</table>

AMPK/ACC—AMP-activated protein kinase/acetyl-CoA carboxylase.
AUC—area under the curve.
G6Pase—glucose-6-phosphatase.
HbA1c—glycated hemoglobin.
HOMA-IR—homeostatic model assessment—insulin resistance.
HOMA β-cell—homeostatic model assessment—beta cell function.
iAUC—incremental area under the curve.
NA—not available/not applicable.
P13/Akt—phosphatidylinositol 3-kinase/Akt (a serine/threonine protein kinase).
PEPCK—phosphoenolpyruvate carboxykinase.
mature adipocytes and adipose tissue (Furuyashiki et al. 2004; Huang et al. 2006; Ejaz et al. 2009; Jung et al. 2014), and has been associated with reduced body weight gain in obese mice (Ejaz et al. 2009).

**Animal studies**

High fat diet-fed mice supplemented with Seapolynol™ (1.25, 2.5 or 5 mg/ day) or isolated dieckol, from *Ecklonia cava* (0.5, 1 or 2 mg/day) for 5 weeks exhibited reduced serum total cholesterol (TC), TG and low density lipoprotein cholesterol (LDL-C) levels compared with mice fed a high fat diet only (Yeo et al. 2012). Similarly, in diabetic mice, a dieckol-rich extract from *Ecklonia cava* (0.5 g dieckol/100 g diet) reduced TC levels and free fatty acids (FFAs) after 6 weeks, compared with placebo, reduced TG levels to an extent similar to treatment with rosiglitazone (0.005 g/100 g diet), and increased high-density lipoprotein cholesterol (HDL-C) compared with rosiglitazone treatment (Lee et al. 2012). Doses of 100 mg/kg body weight/day and 500 mg/kg body weight/day of a phlorotannin-rich extract from *Ecklonia cava* (28.2 ± 0.58% polyphenols) also reduced TG and TC levels in obese mice after 12 weeks, compared with mice fed a high fat diet alone, however, there was no change in HDL-C (Eo et al. 2015). A phlorotannin-rich extract (100–250 mg/kg body weight/day) or isolations of the phlorotannins eckol and dieckol (10 or 20 mg/kg body weight/day) from *Ecklonia stolonifera*, were administered to hyperlipidemic rats (Yoon et al. 2008). The phlorotannin-rich extract reduced TG, TC and LDL-C levels and increased HDL-C levels in a dose-dependent manner after 3 days of treatment. Both eckol and dieckol isolations reduced TG, TC and LDL-C levels after 3 days. Dieckol treatment alone produced a greater hypolipidemic effect than lovastatin (50 mg/kg) and increased HDL-C levels in the hyperlipidemic rats after 3 days (Yoon et al. 2008). Conversely, when Park et al (2012) administered polyphenol-rich extracts from *Ecklonia cava*, grown in two different geographical areas in Korea; Jeju and Gijang, to obese mice at 200 mg/kg body weight/day for 8 weeks, treatment with the extract from Jeju had no effect on TC, TG, LDL-C or HDL-C levels. However, the extract from Gijang reduced TC level compared with placebo (Park et al. 2012), highlighting the potential for differences in polyphenol content based on location, even within the same species of algae (Connan et al. 2004; Bocanegra et al. 2009).

**Human studies**

In a randomized controlled trial in 97 overweight adults, consumption of a phlorotannin-rich extract from *Ecklonia cava*, at doses of 72 or 144 mg polyphenols per day, reduced TC levels, LDL-C levels, and TC to HDL-C ratio, in a dose-dependent manner following 12 weeks of treatment, compared with placebo. An increase in HDL-C levels was only observed following the highest dose (Shin et al. 2012). A comparable trial in 80 adults with raised cholesterol (>200 mg/dL TC, or >110 mg/dL LDL-C) demonstrated that consumption of a dieckol-rich *Ecklonia cava* extract (400 mg/day, 8.2% dieckol) for 12 weeks resulted in reduced TC and LDL-C, compared with placebo, without change in TG or HDL-C levels (Choi et al. 2015). Conversely, in a randomized controlled trial of 25 overweight or obese volunteers, no changes were reported in TC, TG, or HDL-C levels following 500 mg of a polyphenol-containing oral supplement (5% polyphenols) daily for 3 months. However, LDL-C levels were reduced following the supplement treatment compared with no change from placebo (Hernandez-Corona et al. 2014).

**Summary**

Similar to the anti-hyperglycemic evidence, marine polyphenols improved dyslipidemia in animal models and in vitro via a number of mechanisms, although results in humans are few and inconsistent (Table 3). Marine polyphenols have potential as an anti-hyperlipidemic agent in humans, but due to factors such as bioavailability and dosing, which differ considerably between humans and animals, further research is required to determine a consistent effect and appropriate dosage and treatment schedule in humans.

**Anti-inflammatory effects**

Increased inflammatory mediators and chronic sub-clinical inflammation are key risk factors for CVD (Osiecki 2004, Willerson and Ridker 2004; Libby 2006; Bahadoran et al. 2013) and promote the progression of long-term complications of diabetes (Elmarakby et al. 2010; Bahadoran et al. 2013; Roy et al. 2013; Jialal and Devaraj 2014; Roy et al. 2015). There are a number of important mediators (tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1)) that play a role in the regulation of inflammation and may be affected by polyphenols. The anti-inflammatory effects of marine polyphenols are presented in Table 4.

**In vitro studies**

Phlorotannin-rich extracts from the seaweeds *Dictyopteris divaricate*, *Dictyopteris prolifera*, *Prioritis cornea*, *Grateloupia lanceolata*, and *Grateloupia filicina* exhibited anti-inflammatory effects on RAW 264.7 macrophages under lipopolysaccharide (LPS) stimulation. All five species strongly inhibited nitric oxide (NO) production after 18 hours, with IC50 of 18.0 μg/mL, 38.36 μg/mL, 38.43 μg/mL, 32.81 μg/mL, and 37.14 μg/mL, respectively. All extracts also dose dependently reduced inducible NO synthase (iNOS) and cyclooxygenase-2 (COX2) protein levels, and decreased secretion of TNF-α and IL-6 cytokines (Yang et al. 2014). Furthermore, all extracts except *Grateloupia lanceolata* reduced secretion of prostaglandin E2 in a dose-dependent manner (Yang et al. 2014). DPHC, isolated from *Ishige okamurae*, also demonstrated anti-inflammatory effects in LPS stimulated RAW 264.7 macrophages. Compared with control conditions, DPHC potently reduced the secretion of the pro-inflammatory cytokine IL-6 through suppression of the phosphorylation of nuclear factor kappa B (NF-κB), down-regulation of the Janus kinase/signal transducers and activators of transcription (Jak2-STAT5) pathway and upregulation of suppressor of cytokine signaling 1 (SOCS1) regulator. However, DPHC had no effect on levels of secreted TNF-α (Kang et al. 2015). Phlorotannins from the brown algae *Fucus distichus*, *Alaria marginate*, *Saccharina groenlandica*, and *Saccharina latissimi*, have demonstrated anti-inflammatory activity in RAW 263.7 macrophages. All extracts inhibited expression of the
pro-inflammatory genes COX2, iNOS, TNF-α, interleukin 10 (IL-10), and MCP-1 (Kellogg et al. 2015). Further refined phlorotannin extracts also reduced expression of toll-like receptors TLR4 and TLR9 (Kellogg et al. 2015).

**Animal studies**
In a rat model, phlorotannins from three different algal species; *Cystoseira crinita* (56.5 mg GAE/g dried sample), *Cystoseira sedoides* (50.3 mg GAE/g dried sample) and *Cystoseira compressa* (61.0 mg GAE/g dried sample), administered at doses of 25 or 50 mg/kg body weight exhibited anti-inflammatory activity against carrageenan-induced rat paw edema in a dose-dependent manner at 1 hour, 3 hours, and 5 hours postadministration. This level of inhibition was similar to that of known anti-inflammatory mediators (300 mg/kg acetylsalicylic of lysine (aspirin) and 1 mg/kg dexamethasone (an anti-inflammatory steroid medication)) (Mhadhebi et al. 2014). Obese mice fed a phlorotannin-rich extract (28.2 ± 0.58% polyphenols) from *Ecklonia cava* five times a week for 12 weeks, at a dose of 500 mg/kg body weight, showed reductions in protein levels of inflammatory markers MCP1, TNF-α, IL-1β, NF-κB and COX2. Whereas mice that received 100 mg/kg body weight only showed reductions in protein levels of NF-κB and COX2, compared with a high fat diet alone (Eo et al. 2015). Another study in high fat diet-induced obese mice demonstrated anti-inflammatory effects of polyphenol-rich extracts from *Ecklonia cava* (79.70 mg/g of polyphenols), from the geographical area of Gijang, Korea (Park et al. 2012). Following doses of 200 mg/kg body weight daily for 8 weeks, the mice showed reductions in mRNA expression levels of TNF-α, IL-1β and F4/80 in the epididymal adipose tissue, compared with mice who received a placebo (Park et al. 2012).

**Summary**
There is evidence that marine polyphenols reduce inflammation in vitro and in animal models in a dose-dependent manner.
Table 4. Anti-inflammatory effects of marine polyphenols.

<table>
<thead>
<tr>
<th>Seaweed species</th>
<th>Polyphenol</th>
<th>Dosage and duration</th>
<th>Subject/medium</th>
<th>Anti-inflammatory effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ishige okamurae</em></td>
<td>Diphlorethohydroxycarmilol</td>
<td>31.2 mg/mL at 6 hours incubation</td>
<td>RAW264.7 Cells</td>
<td>Dose dependently reduced production of IL-6, downregulated Jak2-STAT5, upregulated SOCS1</td>
<td>(Kang et al. 2015)</td>
</tr>
<tr>
<td><em>Fucus distichus,</em> <em>Alaria marginata,</em> <em>Saccharina groenlandica,</em> <em>Saccharina latissimi</em></td>
<td>Phlorotannin sub fraction</td>
<td>25 to 50 μg/mL</td>
<td>RAW264.7 macrophages</td>
<td>Reduced expression of COX2 iNOS, TNF-α, IL-10 and MCP-1 pro-inflammatory genes</td>
<td>(Kellogg et al. 2015)</td>
</tr>
<tr>
<td><em>Dictyopteris divaricata,</em> <em>Dictyopteris prolifera,</em> <em>Proritis corea,</em> <em>Grateloupia lanceolata,</em> <em>Grateloupia filicina</em></td>
<td>Polyphenol-rich extracts</td>
<td>12.5, 25, 50 or 100 μg/mL, 18 hours incubation</td>
<td>RAW 264.7 murine macrophages</td>
<td>Dose dependently reduced NO production, COX2 protein levels, TNF-α and IL-6 cytokines</td>
<td>(Yang et al. 2014)</td>
</tr>
<tr>
<td><em>Cystoseira crinita,</em> <em>Cystoseira sedoides,</em> <em>Cystoseira compressa</em></td>
<td>Aqueous extracts</td>
<td>25 mg/kg body weight (single dose)</td>
<td>Rat paw edema assay</td>
<td>Dose dependently reduced inflammation</td>
<td>(Mhadhebi et al. 2014)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Polyphenol extract (28.2 ± 1.58% polyphenols)</td>
<td>100 or 500 mg/kg body weight for 12 weeks</td>
<td>Obese C57BL/6 male mice</td>
<td>Dose dependently reduced MCP-1, TNF-α, IL-1/β, NF-κB and COX2 protein levels</td>
<td>(Eo et al. 2015)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Phlorofucofuroeckol-A</td>
<td>200 mg/kg body weight for 8 weeks</td>
<td>Obese C57BL/6 mice</td>
<td>Reduced expression of TNF-α, IL-1/β, and F4/80</td>
<td>(Park et al. 2012)</td>
</tr>
</tbody>
</table>

CA—Jeju geographical area, Korea.
COX2—cyclooxygenase-2.
GAE—gallic acid equivalents.
IL-1β—interleukin 1/β.
IL-10—interleukin 10.
IL-6—interleukin 6.
iNOS—inducible nitric oxide synthase.
Jak2-STATS—Janus kinase signal transducer and activator of transcription.
MCP-1—monocyte chemoattractant protein-1.
NF-κB—nuclear factor κB.
NO—nitric oxide.
SOCS1—suppressor of cytokine signaling 1.
TNF-α—tumor necrosis factor α.

(Table 4). To date, there is currently no research that has examined the anti-inflammatory effects of marine polyphenols in humans. Further research to investigate role of marine polyphenols as anti-inflammatory agents, to reduce the chronic low-grade inflammation that contributes to diabetes progression and cardiovascular diseases in humans is warranted (Osiecki 2004; Willerson and Ridker 2004; Libby 2006; Elmearakby et al. 2010; Bahadoran et al. 2013; Roy et al. 2013; Jialal and Devaraj 2014; Roy et al. 2015).

Antioxidant effects

Tissue damage caused by oxidation contributes to the progression and pathogenesis of inflammation, hypertension, and diabetes, and also increases the risk of CVD (Chowdhury et al. 2014; Murugan et al. 2015). Marine polyphenols may have antioxidant effects that protect cellular constituents against oxidative stress and reduce tissue injuries, either by direct free radical scavenging or through enhancing the actions of endogenous reducing agents (Scalbert et al. 2005; Murugan et al. 2015). Much research has been conducted in vitro to examine the antioxidant properties of polyphenol-rich extracts from marine macroalgae (Table 5).

In vitro studies

Phlorotannin extracts from the brown seaweeds Padina antillarum, Caulerpa racemose, and Kappaphycus alvarezii showed high antioxidant activity as measured by β-carotene bleaching. *Padina antillarum* was determined to have the highest total phenolic content as well as ascorbic acid equivalent antioxidant activity (85 mg AA/100g), highest reducing power (85 mg AA/100g), highest reducing power (15.7 ± 2.6 mg GAE/g) according to the ferric reducing antioxidant power (FRAP) assay and highest chelating ability in the ferrous ion chelating (FIC) assay (Chew et al. 2008). Kumar Chandini et al (2008) examined the reducing power and radical scavenging ability of phlorotannin extracts from three brown seaweeds; Sargassum marginatum, Padina tetrasomatica, and Turbinaria conoides. The antioxidant activity of the extracts...
varied depending on the type of extraction solvent used, likely due to variation in the phlorotannins extracted by each solvent. The ethyl acetate extract from *Sargassum marginatum* had the highest total antioxidant activity according to the phosphomolybdenum method (39.62 mg as ascorbic acid equivalents/g extract) and highest 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging activity (23.16%). All three phlorotannin extracts extracted using methanol exhibited dose-dependent antioxidant activity, comparable to that of ascorbic acid and α-tocopherol at similar concentrations (Shibata et al. 2008). Similarly, an extract from *Fucus vesiculosus* of high molecular weight phlorotannins had strong DPPH quenching activity in chemical assay; where the antioxidant activities of the four phlorotannin isolations exerted a dose-dependent protective effect against H2O2-mediated DNA damage, in comet assay, and exhibited free radical scavenging activity (Ahn et al. 2007). The eckol isolation had the highest radical scavenging ability, scavenging 93% of DPPH at 0.25, 0.5, and 1.0 mg/mL concentrations after 2 minutes (Ahn et al. 2007). Likewise, phlorotannins from *Fucus vesiculosus* exhibited reducing power and radical scavenging ability in non-cellular systems, and reduced production of reactive oxygen species

### Table 5. Antioxidant effects of marine polyphenols.

<table>
<thead>
<tr>
<th>Seaweed species</th>
<th>Polyphenol</th>
<th>Dosage and duration</th>
<th>Subject/medium</th>
<th>Antioxidant effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fucus vesiculosus</em></td>
<td>High molecular weight phlorotannins</td>
<td>Concentrations from 0.1 to 5.0 mg/mL</td>
<td>Chemical assay</td>
<td>Strong antioxidant activity</td>
<td>(Wang et al. 2012)</td>
</tr>
<tr>
<td><em>Ishige okamurae</em></td>
<td>Does not name specific polyphenols</td>
<td>Concentrations from 0.1 to 10.0 mg/mL, incubation periods of 10 to 60 minutes</td>
<td>Chemical assay</td>
<td>Dose-dependent antioxidant activity</td>
<td>(Heo and Jeon 2008)</td>
</tr>
<tr>
<td><em>Padina antillarum</em>, <em>Caulerpa racemosa</em> and <em>Kappaphycus alvarezii</em></td>
<td>Does not name specific polyphenols</td>
<td>Incubation periods of 20 minutes to 4 hours</td>
<td>Chemical assay</td>
<td>Strong antioxidant activity</td>
<td>(Chew et al. 2008)</td>
</tr>
<tr>
<td><em>Sargassum marginatum</em>, <em>Padina tetrastomatica</em> and <em>Turbinaria conoides</em></td>
<td>Does not name specific polyphenols</td>
<td>NA</td>
<td>Chemical assay</td>
<td>Dose-dependent strong antioxidant activity</td>
<td>(Kumar Chandini et al. 2008)</td>
</tr>
<tr>
<td><em>Turbinaria conoides</em> and <em>turbinaria ornata</em></td>
<td>Bifuhalol</td>
<td>Concentrations from 1 μM to 26 μM, 30 minute incubation</td>
<td>Liposome system</td>
<td>Strong antioxidant activity</td>
<td>(Shibata et al. 2008)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em> and <em>Ecklonia kurome</em></td>
<td>Eckol, Phlorofucofuroeckol A, 8,8′-dieckol</td>
<td>Concentrations from 1 μM to 30 μM, 7 days</td>
<td>RAW264.7 cell line</td>
<td>Antioxidant activity</td>
<td>(Li et al. 2009)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>7-phloro eckol, 6,6′-dieckol, Phloroglucinol, Ecl, Fucodiphloroethol G, Phlorofucofuroeckol A, Dieckel</td>
<td>Concentrations from 0.25, 0.5 and 1.0 mg/mL</td>
<td>LS178 mouse T-cell lymphoma cell line</td>
<td>Dose-dependent strong (eckol) Antioxidant activity</td>
<td>(Ahn et al. 2007)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Dieckel</td>
<td>Concentrations from 10 and 50 μg/mL, 24 hours incubation</td>
<td>HUVECs</td>
<td>Antioxidant activity</td>
<td>(Lee et al. 2010)</td>
</tr>
<tr>
<td><em>Fucus vesiculosus</em></td>
<td>28.8% polyphenol content extract</td>
<td>Variety of extract concentrations, 1 hour incubation</td>
<td>Activated RAW264.7 macrophages</td>
<td>Antioxidant activity</td>
<td>(Zaragoza et al. 2008)</td>
</tr>
<tr>
<td><em>Ecklonia cava</em></td>
<td>Dieckel</td>
<td>10 and 20 mg/body weight for 14 days</td>
<td>C57BL/KsJ-db/db type II diabetic mice</td>
<td>Antioxidant activity</td>
<td>(Kang et al. 2013)</td>
</tr>
</tbody>
</table>

HUVECs—human umbilical vein endothelial cells.
(ROS) and NO by RAW 264.7 macrophages in a dose-dependent manner (Zaragoza et al. 2008). Li et al. (2009) also showed antioxidant capacity and free radical scavenging activity, in a linoleic acid model system, of 7-phloro eckol, 6,6'-bieckol, phloroglucinol, eckol, fucodiphloroethol G, phlorofucofur-oecol A and dieckol phlorotannin isolations from Ecklonia cava in the RAW 264.7 cell line. Where 6,6'-bieckol, dieckol and fucodiphloroethol exhibited significantly stronger radical scavenging activities compared with the other phlorotannins (Li et al. 2009). Furthermore, when high glucose-induced oxidative stress in HUVECs was treated with 10 μg/mL and 50 μg/mL dieckol, isolated from Ecklonia cava, glucose-induced cytotoxicity and intracellular ROS generation was inhibited, and thiobarbituric acid reactive substances (TBARS) and NO level were reduced after 20 hours of incubation (Lee et al. 2010).

**Animal studies**

In C57BL/KsJ-db/db type 2 diabetic mice, treatment with dieckol from Ecklonia cava at doses of 10 and 20 mg/kg body weight for 14 days, increased, though not significantly, the activity of endogenous antioxidant enzyme superoxide dismutase (SOD), with no effect on the enzymes catalase (CAT) and glutathione peroxidase (GSH-px) (Kang et al. 2013).

**Summary**

Antioxidant activity of marine polyphenols has been demonstrated in vitro (Table 5). Some studies found that marine polyphenol antioxidant activities were comparable to, or stronger than, that of widely used antioxidants ascorbic acid (Shibata et al. 2008; Wang et al. 2012), α-tocopherol (Kumar Chandini et al. 2008; Shibata et al. 2008; Wang et al. 2012), butylated hydroxytoluene (Wang et al. 2012) or catechin (Nakai et al. 2006), in vitro. There is evidence that the antioxidant activity of marine polyphenols may be dose-dependent, but this was not consistently shown. It is worth noting that the concentrations of marine polyphenols tested in vitro are far greater than concentrations that would be present in human blood and tissues. Therefore, despite strong evidence from in vitro studies, antioxidant activity of marine polyphenols is less likely in humans due to comparatively low absorption rates and serum concentrations (Williamson and Manach 2005; Crozier et al. 2009; Lee 2013), however, this has not been investigated.

**Health effects according to algal species**

Phlorotannin-rich extracts from the Ascophyllum nodosum, Ecklonia stolonifera, Fucus vesiculosus, Ishige okamurae, and

### Table 6. Health effects of marine polyphenols according to algal species.

<table>
<thead>
<tr>
<th>Species</th>
<th>Effect</th>
<th>Subject/medium</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ascophyllum nodosum</strong></td>
<td>Anti-hyperglycemic</td>
<td>Chemical assay</td>
<td>(Nwosu et al. 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3T3-L1 adipocytes</td>
<td>(Apostolidis and Lee 2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetic mice</td>
<td>(Zhang et al. 2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-diabetic adults</td>
<td>(Zhang et al. 2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C5C5 myoblasts</td>
<td>(Paradis et al. 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetic rats</td>
<td>(Kang et al. 2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mice</td>
<td>(Kang et al. 2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetic mice</td>
<td>(Park et al. 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-diabetic adults</td>
<td>(Lee et al. 2012)</td>
</tr>
<tr>
<td></td>
<td>Anti-hyperlipidemic</td>
<td>Chemical assay</td>
<td>(Lee and Jeon 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3T3-L1 preadipocytes</td>
<td>(Yeo et al. 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mice</td>
<td>(Yeo et al. 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetic mice</td>
<td>(Lee et al. 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obese mice</td>
<td>(Lee et al. 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overweight adults</td>
<td>(Park et al. 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults with raised cholesterol</td>
<td>(Park et al. 2012)</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory</td>
<td>Obese mice</td>
<td>(Kang et al. 2013)</td>
</tr>
<tr>
<td><strong>Ecklonia cava</strong></td>
<td>Anti-hyperglycemic</td>
<td>Chemical assay</td>
<td>(Iwai 2008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetic mice</td>
<td>(Iwai 2008)</td>
</tr>
<tr>
<td></td>
<td>Anti-hyperlipidemic</td>
<td>3T3-L1 preadipocytes</td>
<td>(Jung et al. 2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperlipidemic rats</td>
<td>(Yoon et al. 2008)</td>
</tr>
<tr>
<td><strong>Fucus vesiculosus</strong></td>
<td>Anti-hyperglycemic</td>
<td>Non-diabetic adults</td>
<td>(Paradis et al. 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemical assay</td>
<td>(Wang et al. 2012)</td>
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<tr>
<td></td>
<td>Anti-hyperlipidemic</td>
<td>RAW264.7 macrophages</td>
<td>(Zaragoza et al. 2008)</td>
</tr>
<tr>
<td><strong>Ishige okamurae</strong></td>
<td>Anti-hyperglycemic</td>
<td>Chemical assay</td>
<td>(Heo et al. 2009)</td>
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<tr>
<td></td>
<td></td>
<td>Diabetic mice</td>
<td>(Heo et al. 2009)</td>
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<tr>
<td></td>
<td>Anti-inflammatory</td>
<td>RAW264.7 Cells</td>
<td>(Kang et al. 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemical assay</td>
<td>(Heo and Jeon 2008)</td>
</tr>
</tbody>
</table>
**Ecklonia cava** macroalgae varieties are the most predominantly tested with relation to their potential health effects. Table 6 outlines the health effects of these algal species. While there are numerous different seaweed species, the research to date has tended to focus on the aforementioned species with a particular emphasis on *Ecklonia cava*, despite it not being a commonly consumed seaweed. Phlorotannins from *Ecklonia cava* have demonstrated all of the health effects examined in this review and are beginning to be tested in human populations (Shin et al. 2012; Choi et al. 2015; Lee and Jeon 2015). Future research is warranted to continue to investigate the health effects of *Ecklonia cava* phlorotannins particularly in human populations, as they show great potential to be used as a functional food ingredient. However, the potential of other species of macroalgae that are not yet as well investigated should not be neglected.

**Limitations**

It is important to measure the bioavailability of marine polyphenols in humans to properly assess their biological functioning (D’Archivio et al. 2007). Most evidence for the biological activity of marine polyphenols to date has been in cultured cells or animal models, which do not account for the effects of other dietary components, or digestion and absorption in humans, and therefore may not represent the biological actions of polyphenols in humans. Thus polyphenols that have exhibited strong biological activity in vitro may not have the same effect in the human body (Crozier et al. 2009; Lee 2013).

The bioavailability of any compound is affected by its ability to cross membranes, withstand pH changes in the gastrointestinal tract and maintain its structural integrity (Barditch-Crovo et al. 1998; Lee 2013). Factors that affect the absorption and metabolism of polyphenols from food include their chemical structure (degree of glycosylation/acylation, molecular size, degree of polymerization) (Bravo 1998; Scalbert and Williamson 2000; Manach et al. 2004; D’Archivio et al. 2007); dietary factors (interactions with proteins and polysaccharides, transit time, intestinal fermentations, biliary excretion) (Manach et al. 2004); behavioral factors (such as smoking) (Higdon and Frei 2003); individual variation in enzyme activity (Higdon and Frei 2003); and whether absorption takes place in the small intestine or colon (Manach et al. 2004; Bahadoran et al. 2013). The multitude of factors that impact on polyphenol bioavailability result in large variations in bioavailability, and thus biological activity, from one polyphenol to another (Scalbert and Williamson 2000; D’Archivio et al. 2007).

During digestion, polyphenols are metabolized in the small intestine, some in the large intestine by colonic microflora, in the liver and other organs whereby they go through numerous structural modifications (Manach et al. 2004; Williamson and Manach 2005; D’Archivio et al. 2007; Bahadoran et al. 2013). Therefore human body tissues are not exposed to polyphenols in their original form (Crozier et al. 2009; Lee 2013), so in vitro studies that examine polyphenol extracts which have not undergone digestion are not a true representation of the activity or concentration of the metabolites present in the human body (Williamson and Manach 2005; Crozier et al. 2009; Lee 2013). Polyphenol studies need to take into account the changes in structure and concentration that occur when the compounds enter the human body (Crozier et al. 2009; Lee 2013). To further complicate the issue, personal variations in intestinal microflora may also impact an individuals’ metabolism and absorption of polyphenols, but this area is not yet well understood (Lee 2013). These issues highlight the need for studies to be performed in humans.

**Conclusion**

Under experimental conditions polyphenols from marine macroalgae have many positive health-related effects. There is strong evidence in cell and animal models for the anti-hyperglycemic, anti-hyperlipidemic, anti-inflammatory and antioxidant effects of marine polyphenols. However, there are currently only five studies known to have investigated the anti-hyperglycemic and anti-hyperlipidemic effects in humans, and none the anti-inflammatory or antioxidant effects. When translating the research to humans it is important to consider that doses given in animal model studies are likely to be much higher than those in human studies and so the same positive effects may not be observed. It is also important to consider the effects of digestion and metabolism throughout the human digestive tract as this may result in the compounds being altered differently to how they may be within an animal or cell model. More research is required to understand the bioavailability of marine polyphenols and mechanisms of action within the human body and how this differs from cell and animal models. Randomized controlled trials should be performed to examine different doses of marine polyphenols and the effects of different types of marine polyphenols on health outcomes in human populations. *Ecklonia cava* has shown great potential as a source of bioactive marine polyphenols, with evidence for anti-hyperglycemic, anti-hyperlipidemic, anti-inflammatory and antioxidant effects, and trials already completed in human populations. However, other seaweed species should not be ignored in the search for functional food ingredients with health benefits.

**Acknowledgments**

None to declare.

**Conflicts of interest**

None to declare.

**ORCID**

Margaret Murray [http://orcid.org/0000-0003-3767-6947](http://orcid.org/0000-0003-3767-6947)

Aimee L. Dordevic [http://orcid.org/0000-0002-0405-3164](http://orcid.org/0000-0002-0405-3164)

Lisa Ryan [http://orcid.org/0000-0002-5505-7130](http://orcid.org/0000-0002-5505-7130)

Maxine P. Bonham [http://orcid.org/0000-0002-4854-1581](http://orcid.org/0000-0002-4854-1581)

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